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2010 : January 2010 - Author Commentaries : Northwestern's Chad Mirkin On Enabling Nanoparticles

## AUTHOR COMMENTARIES - 2010

January 2010



### Chad Mirkin

Science Watch<sup>®</sup> Newsletter Interview

*Occasionally real science plays out just like the movies: A brilliant experiment is followed by a "Eureka!" moment, and a new vision of the future reveals itself. This was the case in 1996 when the Northwestern University chemist Chad Mirkin witnessed a solution of DNA-assembled nanoparticles change from blue to red as it was heated. Almost immediately, says Mirkin, he knew they had invented the enabling technology for a whole new class of medical diagnostics and perhaps even therapeutics.*

[\[+\] enlarge](#)

*Since then, Mirkin's two initial papers on this work—"A DNA-based method for rationally assembling nanoparticles into macroscopic materials," published in Nature in 1996, and "Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles," published in Science a year later—have each been cited more than 1,500 times (see table below). The papers launched Mirkin on a path of technological innovation that is unparalleled in modern chemistry—"A hell of a run," he says. "One high-impact paper after another." According to the latest update of Thomson Reuters Essential Science Indicators<sup>SM</sup> database, based on papers published and cited over the last decade, Mirkin is currently the number-one ranked author in the Chemistry category, with 200-plus papers, more than 18,000 collective citations, and an average of 85 citations per paper.*

*Mirkin, 46, received his bachelor's degree in chemistry from Dickinson College in Pennsylvania in 1986, and his Ph.D. from Penn State just three years later. He did a postdoctoral fellowship with Mark Wrighton's group at MIT. In 1991, he joined the faculty of Northwestern University, where he is now director of the International Institute for Nanotechnology and also the George B. Rathmann Professor of Chemistry, Professor of Medicine, Professor of Materials Science and Engineering, Professor of Biomedical Engineering, and Professor of Chemical and Biological Engineering. In June of 2009, Mirkin was awarded the \$500,000 Lemelson-MIT Prize for his remarkable record of invention.*

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***Mirkin spoke with Science Watch from his office in Evanston and, befitting his travel schedule of giving 50 to 70 lectures a year, a hotel in Southern California.***

**SW:** Tell us about when you realized that the assembly of nanoparticles into materials with DNA was the ideal platform for medical diagnostics.

I had asked two students, Bobby Mucic and James Storhoff, to synthesize some DNA with an alkylthiol, a sulfur-containing group that sticks to gold. We wanted to make gold nanoparticles with DNA on them. The idea was to build materials using the DNA as a construction material, like chemical-specific Velcro. So they synthesized the DNA and worked out the chemistry to immobilize it on gold nanoparticles. They prepared a second batch of particles with a non-complementary sequence. When a third strand was added that could bring together both particles through hybridization, a particle-assembly event took place. I'll never forget this. It was around 11 o'clock at night. Mucic came down to my office and said, "You have to take a look at this. When I mix them together, the solution turns blue. If I put it in the oven, it turns red." This happened because the dispersed particles are red and the assembled particles are blue. What we were watching with the naked eye was, in effect, DNA raveling and forming the double helix and unraveling again when it was heated. At high temperature, the particles dispersed and were red again. Almost immediately, I remarked that this was a new way of detecting DNA, a really simple way of doing so.

We then started to seriously pursue the question of whether these particles offered a better means for detecting DNA. We began a ten-year set of projects, mapping out the fundamental properties. We discovered spectacular probes, not just for DNA and proteins, but for other molecules. The probes have all kinds of advantages for developing high-sensitivity platforms. And not just in terms of how low one can go in detection—detecting the smallest number of DNA strands—but also in the ability to get the right target and differentiate it from all the wrong targets. Certain people have genetic diseases, which are identified by single nucleotide polymorphisms—one incorrect base in their DNA—and these probes show the ability to identify DNA and differentiate from strands with a single incorrect base, with near-perfect selectivity.

**SW:** In 2000, you founded the company Nanosphere Inc., which markets this technology as part of the Verigene System. What's the status of the Verigene System today?

It's a commercialized system, now used in hospitals all around the country. It's in what I call a ramp-up stage. The company has four FDA-cleared diagnostic tests, panel tests that are used for diseases from cystic fibrosis to flu to predisposition to thrombosis—for detecting people who have a genetic predisposition to blood clotting—to a warfarin (blood thinner) metabolism assay. It turns out that a significant number of people have a genetic inability to metabolize warfarin, and this can lead to major problems in terms of dosing them properly. If they're not metabolizing the warfarin, the more you give them, the more their blood thins. There are other ways of doing DNA detection or genetic-based analysis, but the Verigene System allows one to perform the analysis at the point of care. It's fast and accurate and doesn't require a great deal of expertise or complicated and expensive equipment. So instead of sending samples to remote labs, the user can analyze them, for example, in a hospital. It cuts out a middle man, gets the information to the doctor in a shorter time, and does a lot of good for the patient. It's a major step towards point-of-care molecular diagnostics.

**SW:** You've suggested that this nanoparticle technology can be used for gene regulation as well as diagnostics. Is this the next step?

It's the next big hurdle: moving this from diagnostics to therapeutics. We're now using these particles to go into cells and turn off cancer genes, to turn off all sorts of diseases, so you can think about enabling a whole new platform of gene-therapy systems—systems that turn out to be non-toxic and highly effective in terms of their ability to regulate these types of processes.

**SW:** Can you give us an example of how this might work?

Cancer is an obvious one. Cancer cells often over-express a gene called survivin, which produces a set of proteins that stop the cell from dying—they stop apoptosis. That's what makes cancer cells immortal. So the idea here is to design particles that can go into these types of cells and turn off each cell's ability to produce those kinds of proteins, and therefore make it more like a healthy cell that can then die via apoptosis.

**SW:** Do you have to specifically target the cancer cells?

The particles go into all cells, but only the cancer cells over-express this particular type of gene. And that's where the non-toxicity comes into play. Because the particles aren't toxic, you can flood an area. One of the cancers we're looking at is glioblastoma, a brain cancer. A surgeon takes out a lethal tumor. If he leaves even a few cells behind, that patient is likely going to die. In fact 95% of these patients do die within five years. So the question is, how do you make sure you clean up the last few cells? Well, here we're going to flood the area, and all the cells in the local area will pick up these particles. But we will target the cancer cells at the genetic level and therefore selectively kill them. We're targeting genes that are unique in cancers cells, so healthy cells will be unaffected.

Don't get me wrong, though—it's a long way away. It's too far right now to call it a real therapeutic. But these particles look extremely promising. The beauty is that they don't require toxic materials to get into cells. All the other systems that have been tried require the use of highly toxic lipid and polymer carriers. Our particles naturally go into cells and do so in a very stealth manner. Moreover, they can get the job done in a highly selective fashion based on this genetic triggering.

**SW:** How do the nanoparticles get into the cells? Are they just small enough to slip through the membranes?

It's not just their size—it's what's on their surface. Their surface chemically triggers something called endocytosis; it makes the cell pick them up. These particles are made of gold and are decorated with

Highly Cited Papers by Chad A. Mirkin and Colleagues, Published Since 1996 (Ranked by total citations)		
Rank	Papers	Cites
1	C.A. Mirkin, <i>et al.</i> , "A DNA-based method for rationally assembling nanoparticles into macroscopic materials," <i>Nature</i> , 382 (6592): 607-9, 1996.	1,882
2	R. Elgarian, <i>et al.</i> , "Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles," <i>Science</i> , 277(5329): 1078-81, 1997.	1,473
3	R.D. Piner, <i>et al.</i> , "'Dip-pen' lithography," <i>Science</i> , 283(5402): 661-3, 1999.	1,187
4	R.C. Jin, <i>et al.</i> , "Photoinduced conversion of silver nanospheres to nanoprisms," <i>Science</i> , 294(5548): 1901-3, 2001.	1,032
5	T.A. Taton, <i>et al.</i> , "Scanometric DNA array detection with nanoparticle probes," <i>Science</i> , 289(5485): 1757-60, 2000.	981

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DNA strands. The DNA is used for two purposes. One is to trigger the endocytosis; it actually causes the pick-up of signaling proteins from the extracellular matrix. But the DNA is also the genetic-regulation mechanism. It goes in and is designed to bind to mRNA, which then shuts down the ability of that cell to produce a specific protein that the mRNA encoded for. The particles also can deliver SiRNA, another potent nucleic acid-based gene-regulation material. This is the next wave. We've actually developed a new company, AuraSense, to develop the particle platform.

**SW: How long do you think it will take for this technology to come to fruition, if it does?**

It's hard to predict, but I hope that within five to seven years, we'll have some very strong candidates for new kinds of therapies for oncology.

**SW: In what other areas of medicine do you see this having an impact?**

Well, that's also the beauty of it. You can begin to think about targeting any disease that has a genetic basis, and a lot of diseases do. Cure is in the cards in certain cases; managing is definitely in the cards.

**SW: How much do you still consider yourself a chemist and how much a medical researcher?**

I'm first and foremost a chemist. But my group at Northwestern does everything. We've gone from chemistry all the way through materials science and engineering and medicine. The group consists of roughly 50 people, and there are a lot of chemists, but also many biologists now, several materials scientists, and even a couple of medical doctors. And that doesn't include the researchers we have at the three companies we've created—a workforce of over 200 people working on these problems.

**SW: What are you working on now that you're really excited about but haven't yet published?**

On the pure chemistry side of things, what we want to do is learn how to make molecules that do what PCR [the polymerase chain reaction] does, but for things other than nucleic acids—asking the question, how can one synthesize molecules that can recognize other molecules and make more of them? PCR is an incredibly powerful technology, but it only works for nucleic acids. Therefore, one of the grand challenges is to design molecules that have nothing to do with biology but are inspired by biology: they will be able to do what PCR does, and allow one to recognize a small molecule—say, a medically relevant diagnostic indicator—and trigger some sort of conformational change that then turns over a catalytic reaction that generates more of the molecule that the complex originally recognized. In this way, one can create a cascade-amplification system, which has all sorts of implications for diagnostics and therapeutics. If you look at what PCR did for molecular biology and medicine, it really changed the way we think about what we can detect. With PCR, researchers can now analyze and identify a few molecules in a sample. Before PCR, those molecules would have passed beneath the radar screen of the conventional diagnostic tools we had at the time. I now want to be able to develop the chemistry, and then ultimately the technology, to create similar capabilities for other molecules beyond nucleic acids.

**SW: Your other great innovation, the one that cemented your reputation, was dip-pen lithography. Can you tell us how that came about?**

Dip-pen was interesting. We weren't trying to create a lithographic tool when we invented it. We were actually studying water transport from an AFM [atomic force microscope] tip to a surface. It was hypothesized for a long time that when you bring a tip in contact with a surface in air, water will collect at the point of contact. That's called the capillary effect. It turns out that that's a thermodynamic minimum

for water in the system; that's the energetically preferred site for the water.

I had a post-doc, Richard Piner, who was studying this water-transport process. He was a pipe smoker, and during a routine experiment he left the AFM tip in contact with the surface and went outside to smoke his pipe, and when he came back, he pulled the tip away and did a survey scan of the surface and saw what looked like a droplet. That droplet turned out to be water. And that's the first time anybody had actually imaged what's called the meniscus—the droplet of water that forms at the point of contact between tip and surface. He then discovered that when you move the tip across the surface, one of two things happens: either you deposit water on the surface or you deplete water from the surface. You create either a raised pattern or a recessed pattern from that water transport. That's temporary—eventually, it simply fades away as everything returns to equilibrium. And Richard, being a physicist, thought this was absolutely fascinating, and it was.

*"One of the grand challenges is to design molecules that have nothing to do with biology but are inspired by biology," says Chad Mirlin of Northwestern University, Evanston, Illinois."*

But, as I told you earlier, I'm a chemist at heart. I said, "Richard, this is fascinating, but nobody's going to be really interested in it, at least from the chemistry side, unless we can actually make something with it. So why not try to put molecules on that tip; say, alkanethiols, and see if they transport to gold, and use the little droplet of water—turning a lemon into lemonade—as a transport vehicle." Now, if we move the tip across the surface, the molecules can move across or through the water, and if they have a functional group that can react with the surface, they'll form a single layer on the surface that should be stable and should last for a long time. And that was really the birth of dip-pen nanolithography. Later, we found that this process is highly controllable, and in fact you can use environmental humidity and the water as a way of regulating how fast the molecules move from tip to surface.

So, with water-soluble molecules, you can ratchet up the humidity and increase their rate of transport or you can ratchet it down and decrease it. And, in fact, the commercial systems that are now sold are in controlled-humidity chambers. Then we started thinking about all of the different things one can do with dip-pen, looking at the mechanisms of transport, and it really gave birth to a whole area of nanoscale molecular printing that now involves the patterning of just about everything from DNA to proteins to viruses to small molecules to catalysts to really anything one would like to study on the nanoscale. It's become, I think, one of the workhorse tools, if not *the* workhorse tool, for nanotechnologists to study the consequences of miniaturization and how chemically controlled surfaces and interfaces can be used to study and regulate many processes in chemistry and biology.


**SW: Considering that you now have over 350 patents and technological innovations spanning, as you say, a wide variety of fields, do you have a philosophy of invention that you can tell us about?**

**A way of thinking about problems that leads to innovation?**

I see it as similar to composing. You get in, you start looking—for instance, at some of the unusual characteristics of materials, unusual properties—and you just connect the dots. You say, "How can I use those new properties for developing tools that will make a difference? Not just another way of doing things, but a much better way of doing things?" I think that's where a lot of people miss the boat. The world doesn't want just another way of diagnosing or treating disease—it wants a better way of doing it. So you really have to see what the analytical benchmarks are, what the current ones are, and how you can exceed them with the new properties or the new materials you're making. ■

KEYWORDS: CHAD MIRKIN, NORTHWESTERN UNIVERSITY, NANOPARTICLES, NANOTECHNOLOGY, SILVER  
NANOSPHERES, GOLD NANOPARTICLE, NANOPARTICLE PROBES.

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